1: Eur J Pain. 2002;6(4):261-72. Related Art

ELSEVIER FULL-TEXT ARTICLE

Gabapentin and pregabalin suppress tactile allodynia and potentiate spinal cord stimulation in a model of neuropatl

Wallin J, Cui JG, Yakhnitsa V, Schechtmann G, Meyerson BA, Lir B.

Department of Clinical Neuroscience, Section of Neurosurgery, Karolinska Institutet, S-171 76 Stockholm, Sweden.

Spinal cord stimulation (SCS) is an effective tool in alleviating neuropathic pain. However, a number of well-selected patients obtain satisfactory pain relief. Previous studies have demonstrat i.t. baclofen and/or adenosine can enhance the SCS effect, but tl combined therapy has been shown to be useful in less than half cases and more effective substances are therefore needed. The this experimental study in rats was to examine whether gabaper pregabalin attenuates tactile allodynia following partial sciatic n injury and whether subeffective doses of these drugs can potent effects of SCS in rats which do not respond to SCS. Mononeuro was produced by a photochemically induced ischaemic lesion of sciatic nerve. Tactile withdrawal thresholds were assessed with Frey filaments. Effects of increasing doses of gabapentin and pregabalin (i.t. and i.v.) on the withdrawal thresholds were analy These drugs were found to reduce tactile allodynia in a dose-dependent manner. In SCS non-responding rats, i.e. where stimu per se failed to suppress allodynia, a combination of SCS and subeffective doses of the drugs markedly attenuated allodynia. I subsequent acute experiments, extracellular recordings from wi dynamic range neurones in the dorsal horn showed prominent hyperexcitability. The combination of SCS and gabapentin, at th subeffective dose, clearly enhanced suppression of this hyperexcitability. In conclusion, electrical therapy and pharmac therapy in neuropathic pain can, when they are inefficient indivi become effective when combined. Copyright 2002 European Fe of Chapters of the International Association for the Study of Pai Published by Elsevier Science Ltd.

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Albany Molecular Research, Inc.
21 Corporate Circle, Albany, NY 12203 USA · Tel: 518-464-0279 · Fax: 518-464-0210

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Trip Report: Residential School on Medicinal Chemistry Madison, New Jersey June 11-15, 2001

Shuang Liu, Ph. D.
Medicinal Chemistry
Albany Molecular Research, Inc.
21 Corporate Circle
PO Box 15098
Albany, NY 12212-5098

Abstract. The 15th "Residential School on Medicinal Chemistry" was held at Drew University in Madison, New Jersey from June 11 to June 15, 2001. There were about 200 attendants this year, most of them have synthetic chemistry backgrounds and are currently working as medicinal chemists in pharmaceutical and biotech companies. The speakers were experts from pharmaceutical/biotech industry and universities. The purpose of the school was to give an overview of the fundamental principles of Medicinal Chemistry as well to highlight the latest trends in drug research and development. The program material is available at the west campus library.

This year's program included eighteen lectures, three seminars and three case history reviews (see table). This trip focuses on the new material covered in the school.

Lecture 1	Strategies in Drug Discovery	Manfred Wolff, Intellepharm
Lecture 2	Principles of Pharmacological Assays	Joseph Cannon, University of Iowa
Lecture 3	Drug Metabolism	Patrick Murphy, Butler University
Lecture 4	Control of Ion Transport	David Triggle, SUNY-Buffalo
Lecture 5	Transporter Regulation	Wolfgang Sadée, University of California, San Francisco
Lecture 6	Genomics: New Paradigms for Small Molecule Drug Discovery"	Martin Rosenberg, SmithKline Beecham

Lecture 7	"Receptor Binding Assays"	Michael Williams, Northwestern University School of Medicine
Lecture 8	"Receptor Structure and Agonist-Antagonist Assays"	P.B.M.W.M. Timmermans, Tularik, Inc.
Lecture 9	"Enzyme Inhibitors"	Richard Silverman, Northwestern University
Lecture 10	"Structure Based Drug Design"	Jonathan Greer, Abbott Laboratories
Lecture 11	"QSAR in Drug Research"	Allan Ferguson, Rosetta Inpharmatics
Lecture 12	"Cell Based Assays"	Mark Goldman, Neurogenetics, Inc.
Lecture 13	"Chemical Diversity"	Philip Hughes, Sphinx/Lilly
Lecture 14	"Peptidomimetics"	Roger Freidinger, Merck
Lecture 15	"High Throughput Screening"	Matthew Sills, Novartis
Lecture 16	"Drug Delivery"	David Friend, Delsys Pharmaceuticals
Lecture 17	"Toxicology"	Vincent Traina, Traina Consultants
Lecture 18	"Patents"	Manfred Wolff, Intellepharm
Seminar I	"Molecular Modeling"	Jonathan Greer, Abbott Laboratories
Seminar II	"Pharmacokinetics and ADME"	Elizabeth Topp, University of Kansas
Seminar III	"Lead Structure Development"	Richard Silverman, Northwestern University
Case History	"Discovery and Development of Pregabalin"	David J. Wustrow, Pfizer Global R&D
Case History	"Design and Synthesis of Rapamycin Analogs: The Discovery of CCI - 779, a Novel Anti-Tumor Agent With a Unique Mechanism of Action"	Jerauld S. Skotnicki, Wyeth-Ayerst
Case History	"The Discovery of Linezolid, A Novel Antibacterial Agent"	Michael R. Barbachyn, Pharmacia

"Case History of Gabapentin and Pregabalin"

David J. Wustrow (Pfizer).

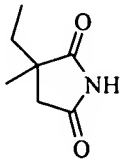
Dr. David J. Wustrow presented the discovery and development of Gabapentin and Pregabalin, both of which are anticonvulsants with novel mechanisms of action.

Introduction:

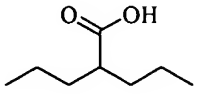
Over 50 million people worldwide suffer from epilepsy, 2.5 million of these individuals are in the US where 125,000 new cases are diagnosed every year. The existing antiepileptic drugs provided incomplete control of seizures in 20-25% patients, as well as induce unwanted side effects. The agents act by general blockade of neuronal sodium and calcium channel thereby inhibiting neural transmission. Careful dose titration is required to avoid dangerous side effects such as ataxia and cognitive function, which arise from the depression of the central nerve system. In addition, these agents produce a variety of side effects not directly related to their mechanism of action including agranulocytosis, hepatotoxicity, aplastic anemia, serious rash and nausea.

Figure 1
Stardard Antiepileptic Drugs

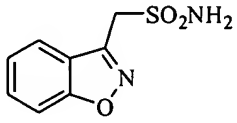
T-Type Calcium Channel Blockers



Ethosuximide

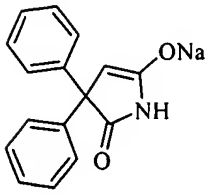


Valproic Acid

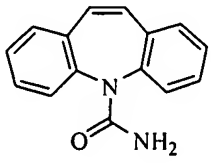


Zonisamide

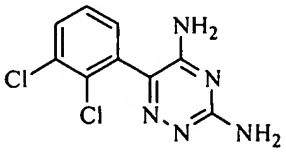
Sodium Channel Blockers



Phenytoin Sodium



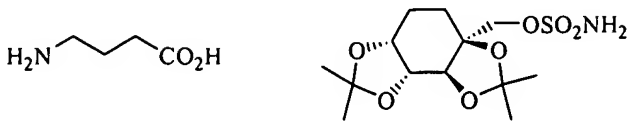
Carbamazepine



Lamotrigine

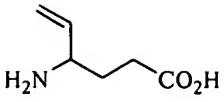
An alternative mechanistic approach to anticonvulsant activity is to potentiate the effects of inhibitory neurotransmission system. The most important of these systems are those associated with inhibitory neurotransmitter ?-amino butyric acid (GABA). Examples of drugs acting through GABA pathway include topiramate, which potentiates the action of GABA at $GABA_A$ receptor; tiagabine, which increases synaptic GABA concentration by binding to GABA reuptake sites; and vigabatrin, which prevents GABA degradation.

Figure 2
Some GABAergic Drugs

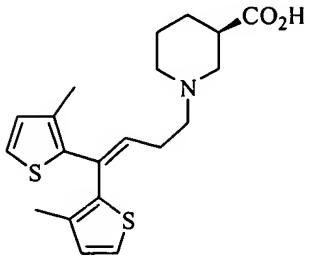


GABA

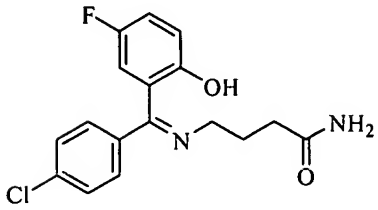
Topiramate



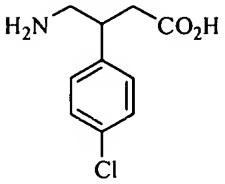
Vigabatrin



Tiagabine



Progabide



Baclofen

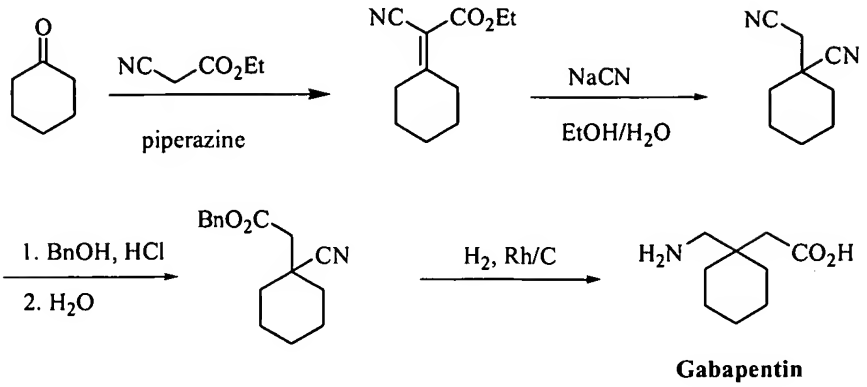
Discovery and Development of Gabapentin (Trade Name Neurontin)

A strategy utilized in the design of early GABAergic drug was to manipulate the molecule of GABA so as to increase its log P and thereby allow it to gain access to the CNS. This principle was applied in a simple form in the design of series of GABA derivative wherein the third carbon atom of GABA is incorporate into a cycloalkyl ring varying from 5-8 carbon atoms. When these compounds were assessed preclinically against seizures induced by thiosemicarbizide or electric shock, the six membered ring compound was found to be most effective. This compound became known as gabapentin.

Gabapentin, however, was shown not to bind to $GABA_A/GABA_B$ receptors, GABA reuptake sites or inhibit GABA transaminase. Radiolabeling study revealed that gabapentin bind to a protein in rat brain that was identified to be the ? 2? subunit of voltage gated calcium channels. This subunit enhances the efficiency with which calcium ions are conducted through the main pore, which forms a unit of the calcium channel. The interaction of gabapentin with this subunit is associated with the reduction of neurotransmitter release from stimulated neuronal tissues.

While gabapentin is somewhat more lipophillic than GABA, the Log D of gabapentin is at least 2 log units lower than the range generally accepted as being optimal for passive diffusion across the blood brain barrier. It is unlikely that the change in Log P alone accounted for the brain levels of gabapentin that were observed after systemic administration. It was found that the incorporation of the cyclohexane ring enforced a folded conformation of the GABA chain, which is recognized by the system L neutral amino acid transporter. In this way, the GABA chain was indeed responsible for the compound crossing the blood brain barrier although in an unexpected way.

Scheme 1
Synthesis of Gabapentin



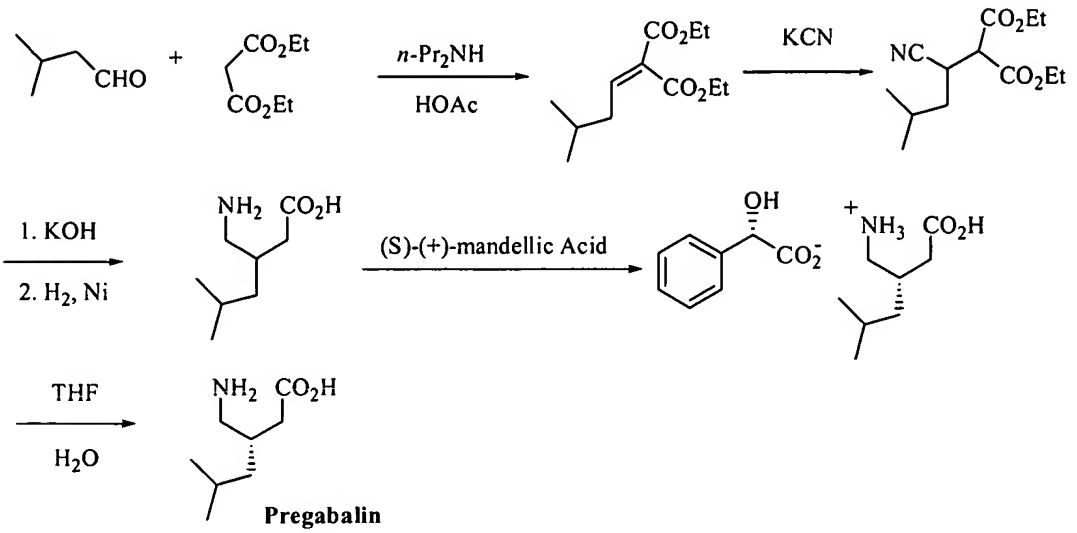
Gabapentin

Discovery and Early Development of Pregabalin.

Professor Richard Silverman and co-workers at northwestern University prepared a series of racemic 3-substituted GABA analogs as L-glutamic acid decarboxylase enhancers. Several of these analogs were tested at Pfizer (then Park-Davis; Warner-Lambert) for their ability to inhibit maximal electroshock induced seizures in mice. Of the compounds showing anticonvulsant activity, by far the most potent was the 3-isobutyl GABA analog. Subsequent binding and transport studies revealed that the S isomer was more potent that the R isomer in the ? 2??binding assay (IC_{50} 80 vs 950 nM) and at inhibiting System L mediated leucine transport (IC_{50} 158 vs 350 ?M). The anticonvulsant activity was also found to exist solely in the S isomer that became known as pregabalin. Like gabapentin, pregabalin was also found to inhibit the stimulated release of norepinephrine and glutamate. Further preclinical and early development studies with pregabalin showed two differences between gabapentin and pregabalin. Pregabalin possessed greater in vivo potency and had a more linear relationship between dose and plasma levels of drug than gabapentin. Pregabalin was, therefore, taken into development as an anticonvulsant agent.

Scheme 2

Process Synthesis of Pregabalin



Clinical Studies with Gabapentin and Pregabalin

Double blind, placebo controlled clinical studies using gabapentin as an add on therapy to existing antiepileptic drugs were carried out and showed that gabapentin taken at 1200-1800 mg/kg per day was well tolerated and caused a significant decrease in the number and severity of seizures. Gabapentin (trade name Neurontin) is approved worldwide as an add-on treatment of epilepsy. It is an ideal drug to be used in combination with other medications as gabapentin is not metabolized, it does not change the metabolic profiles of co-administrated compounds. In summary, gabapentin and pregabalin are well-tolerated anticonvulsant agents, which operates through a novel mechanism of action.

Gabapentin and Pregabalin against Neuropathic Pain and Anxiety

Neuropathic Pain is chronic pain that is brought about by damage to sensory neurons that caused an abnormally excessive response to noxious stimili. These pain states do not respond to opioid or NSAID (non-steroidal anti-inflammatory drugs) treatment. Like some other anticonvulsants, both gabapentin and pregabalin were shown to have clinical activity against neuropathic pain in various animal models. High doses of gabapentin were shown to be active in large clinical trial trials against neuropathic pain induced by diabetic neuropathy and postherpetic neuralgia. Gabapentin has been registered in Germany, France and England for the treatment of neuropathic pain. Gabapentin and pregabalin have also been evaluated in preclinical models of anxiety and both have shown promising activities. Patients who received gabapentin in a clinical trial against social phobia showed a statistically greater decrease on the Liebowitz Anxiety Scale.

"Case History of Linezolid"
Michael R. Barbachyn (Pharmacia Corporation).

Dr. Michael Barbachyn presented the discovery and development of Linezolid, a novel antibacterial agent.

Introduction

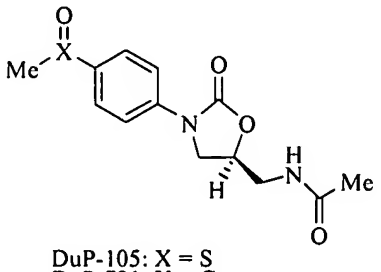
The development of bacterial resistance to currently available antibacterial agents is a growing global health problem. Of particular concern are infections caused by multidrug-resistant gram-positive pathogens. Principal players among these problematic organisms are isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE), vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VREF), and also penicillin- and cephalosporin-resistant *Enterococcus pneumoniae*. These pathogens are responsible for significant mortality in both the hospital and community settings. A number of MRSA isolates were recently identified and found to have reduced susceptibility to vancomycin. No effective treatment exists for infections caused by such strains.

The most common approach to solve the problem of bacterial resistance is to modify the existing classes of antibacterial agents to provide new analogs with improved attributes. Another successful strategy is to combine existing antibacterial agents with other drugs. Improved diagnostic procedures may lead to rapid identification of the causative pathogen and permit the use of narrow spectrum antibacterial agents. In addition, the utilization of adjuvant therapies, such as immune system modulators or compounds targeting virulence gene products, is an emerging area with significant potential. Finally, and most importantly, the discovery of novel class of antibacterial agents employing new mechanisms of action has considerable promise. Such agents should exhibits a lack of cross-resistance with existing antimicrobials.

Emergence of the Oxazolidinones

In 1987, DuPont reported the structure and antibacterial activity profiles of two new antibacterial agents, DuP-105 and DuP-721.

Figure 3

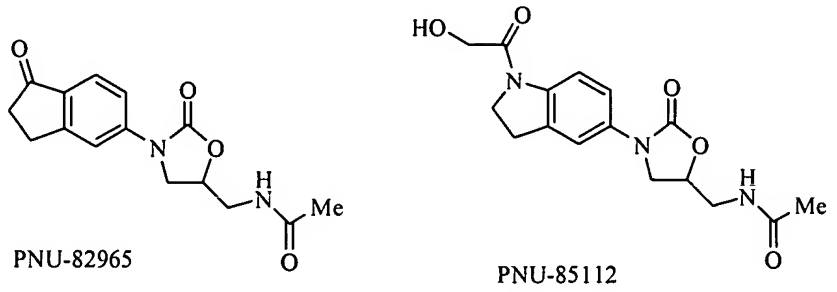


DuP-105: X = S
DuP-721: X = C

The DuPont compounds were the first significant representatives of a totally novel class of antimicrobials, the oxazolidinones. The oxazolidinones employ a unique mechanism of action

involving inhibition of the initiation phase of bacterial protein synthesis. However, Dup-105 and Dup-721 only briefly entered into phase I clinical trials and were withdrawn because of concern about their safety profiles. Meanwhile, Pharmacia (then The Upjohn Company) initiated an exploratory oxazolidinone program and identified two oxazolidinone analogs, (+/-)-PNU-82965 and (+/-)-PNU-85112, which exhibited excellent safety profiles in essentially identical rodent studies. A structure-toxicity relationship was identified for the oxazolidinones.

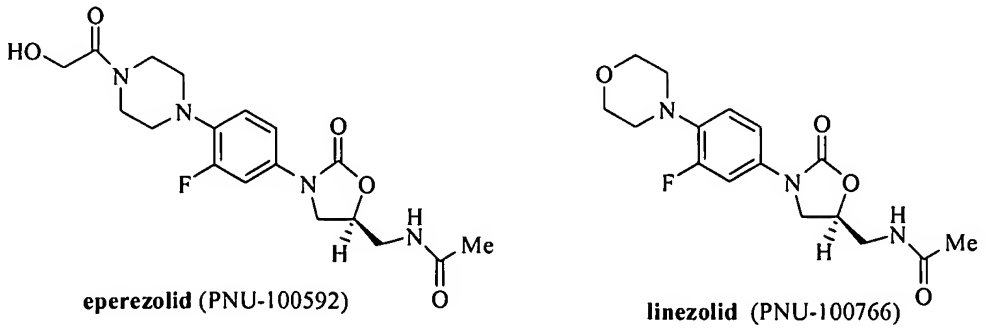
Figure 4



PNU-82965 PNU-85112

The Pharmacia group then expanded their chemistry effort and thoroughly explored the structure-activity relationships of these compounds. The team discovered that some N-C linked saturated heterocyclic rings attached to the 4-position of the phenyloxazolidinone pharmacophore exhibited excellent antibacterial activity and efficacy while maintaining a suitable safety profile. A further significant finding was that one or two fluorine substituents on the phenyl ring, flanking the appended heterocyclic ring, conferred enhanced properties to the analogs. Another development at this time was the identification of an efficient and general procedure for preparing the desired oxazolidinone analogs in enantiomerically enriched form. These efforts resulted in the first clinically successful oxazolidinones, eperezolid (PNU-100592) and linezolid (PNU-100766).

Figure 5



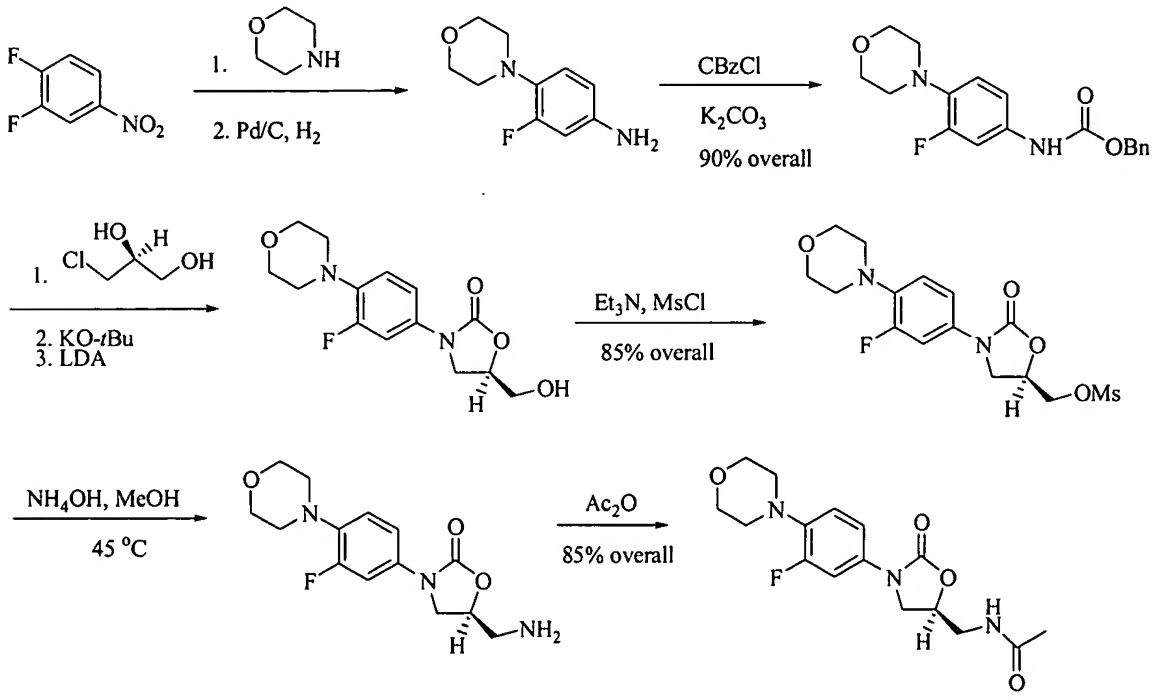
eperezolid (PNU-100592) **linezolid** (PNU-100766)

Linezolid was recognized as a potentially important new therapeutic agent for the treatment of infections caused by dram-positive bacterial. Importantly, linezolid's spectrum of activity includes multidrug-resistant strains of the *Staphylococci*, *Streptococci* and *Enterococci*, including a recent isolated glycopeptide-intermediate *Staphylococcus aureus* (GISA) which has reduced susceptibility to vancomycin.

Eperezolid and linezolid entered clinical trials in 1994 and 1995, respectively. It rapidly became apparent that linezolid exhibited a superior pharmacokinetic performance profile in human subjects that would permit a BID dosing regimen. Linezolid was chosen over eperezolid as for study in advanced clinical trials. The compound subsequently demonstrated excellent efficacy in various phase III studies. An NDA was submitted to the FDA on October 18, 1999 and linezolid, marketed as Zyvox, was approved on April 18, 2000. Preliminary indications include: (1) infections caused by vancomycin-resistant *Enterococcus faecium*, including cases with concurrent bacteremia; (2) complicated and uncomplicated skin and skin structure infections; and (3) nosocomial and community-acquired pneumonia.

Scheme 3

Process Synthesis of Linezolid (PNU-100766)



linezolid (PNU-100766)

